Fra Discussion:

our previous studies (data not shown). In conclusion certain parts of the innate immune system may either be activating directly the expression of the *tra* genes of the R plasmid or through the stress response of the bacterial host to the activated innate immune system of the animal host.

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Interestingly meloxicam seems to have the opposite effect compared to the probiotic bacteria on the expression of the *tra* genes of pRAS1. These opposite effects of the two treatments on the expression of the tra genes of pRAS1 may be used to identify specifically which part of the innate immune system of the animal host that stimulate the *tra* gene expression in pRAS1. In our *in vitro* conjugation studies meloxicam addition didn't change conjugation frequency. There are no known studies on the impact of the NSAIDs on horizontal gene transfer among the bacteria within an infected host, so far. Meloxicam is a non-steroidal agent of the oxicam class and its anti-inflammatory action has been described in pigs challenged with endotoxin [38]. Meloxicam acts by inhibition of cyclo-oxygenase which catalyses the first step of the decomposition of arachidonic acid to prostaglandins, prostacyclin and thromboxane. Inhibiting the synthesis of these mediators, meloxicam breaks the chain of prostaglandin-induced endotoxin effects which are not targeted by antibiotics. Reduced inflammation in intestine can be linked to the reduced mobility gene activities on R-plasmid. The possible boost effect of inflammation on horizontal gene transfer in the gut between a pathogenic and a commensal Enterobacteriaceae bacterium has recently been demonstrated [39].

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An equally remarkable finding was the impact of antibiotic treatments on the acute phase protein CRP, which is a non-specific marker for disease, and therefore can be used to detect a wide range of insults that induce an inflammatory response. In pigs with an ongoing febrile or inflammatory response, CRP levels can rise by 100-fold and is the most responsive acute

phase protein in an inflammatory situation studied thus far in the pig [40]. The decreased CRP in the piglets' blood after non-effective Terramycin® treatment are in accordance with earlier reports [41, 42] that tetracyclines cause posttranscriptional blockage of cytokine production [43]. Whereas, Zoolac® and Zoolac®+Metacam® treatments that have no impact on the growth of pathogenic *E. coli*, had little impact on the serum proteins, as expected. In contrast, the sub-inhibitory level of Baytril® caused increase in the levels of the CRP. Effective Baytril® treatment caused an even higher expression of this serum parameter. It may be related to the diminished number (killed) of pathogenic *E. coli* that can no longer depress the immune system by its virulence factors [44, 45]. The ineffective treatment with low concentration of Baytril® has diminished the bacterial flora at a low level which was not seen with tetracycline treatment. Hypothetically, it can be explained by immunomodulatory properties of those drugs [20]. In our study combinations of effective antibiotics with probiotics showed even higher immunomodulation effect.

An unexpected result in this study is the histopathological observation that ETEC infected piglets given probiotic bacteria seem to get a reduced number of neutrophilic immune cells in the lamina propria even also compared to the negative uninfected control piglets. This effect was not seen with any of the other treatments. It can be speculated that the stimulating effect of probiotic bacteria on the innate immune system modulates the parts of the mucosal immunity that is related to occurrence of neutrophils in the gut wall. This phenomenon seems clear and most probably has a clinical impact on the outcome of the infection.

The observation that there are no bacteria or a very limited number linked to the mucosa when a therapeutic concentration of Baytril[®] was used in the infected piglets is as expected for a drug that is believed to kill the bacterial pathogen directly *in vivo* as seen *in vitro*. However,